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| 10/826,478      | 04/16/2004  | Mingjie Zhang        | WILKG5.001AUS       | 1295             |

20995 7590 03/27/2007  
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| EXAMINER |
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PETERSEN, CLARK D

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| ART UNIT | PAPER NUMBER |
|----------|--------------|

1657

| SHORTENED STATUTORY PERIOD OF RESPONSE | NOTIFICATION DATE | DELIVERY MODE |
|--|-------------------|---------------|
| 3 MONTHS                               | 03/27/2007        | ELECTRONIC    |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/27/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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## Office Action Summary

Application No.

10/826,478

Applicant(s)

ZHANG ET AL.

Examiner

Clark D. Petersen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 25 December 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-9 and 12-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9 and 12-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

This action is in response to the amendment, filed 25 December 2006, in which claims 1-3 and 17-22 were amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All objections and rejections not repeated in the instant Action have been withdrawn due to Applicant's response to the previous Action.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This is a new rejection necessitated by Applicants' amendment.

It is not clear what is meant by "free PDZ domain"; for example, the term "free" could mean either not bound to any substance, or it could mean a PDZ domain isolated from a whole protein, i.e. a truncation or an isolated domain lacking other structural features of the wildtype protein.

Appropriate correction is required.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 16-19, 21, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Tochio et al (J Mol Biol, 2000).

This rejection is maintained for reasons of record set forth in the paper mailed 25 September 2006, and repeated below.

Tochio et al teach a method of testing the effect of a potential binding partner of PDZ2 of PSD-95. In particular, they test the effect of binding of a peptide that is a C-terminal fragment of the protein CAPON (see Results and Discussion, p. 227 col. 2, for example). The binding of CAPON to a <sup>15</sup>N-labeled PSD-95 PDZ2 was used to compare the bound vs. unbound conformation of PSD-95 PDZ2. From these data, a chemical shift figure was generated (see Fig. 5, p. 231, for example). In particular it was noted that CAPON binding induced strong shifts in  $\alpha$ B and  $\beta$ B of PSD-95 PDZ2 (see p. 228 col 1, for example). In particular, the residues GLGF, which are residue numbers 169-172, undergo a large chemical shift in response to binding by a ligand (see text, p. 227 col 1; see Fig. 5, p. 231, as examples). The sequence used in the experiments was that of rat PSD-95 PDZ2 (see Materials and Methods, p. 232, col 1, for example), which is the protein of SEQ ID NO:4 in the instant application. This sequence has greater than 50% homology to human PSD-95 PDZ2 as well. Furthermore, due to their strong

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sequence similarity, the analogous rat and human PSD-95 full length as well as isolated PDZ2 (i.e. SEQ ID Nos: 1, 3, 5 and 7) nucleic acid sequences would bind to each other in a stringent Northern blot.

***Response to arguments - 35 USC § 102***

Applicants traverse the rejection of claims 1-3, 16-19, 21, and 22 under 35 USC 102(b) as being improper. Applicants argue that the Tochio reference does not teach each and every step of the instant claims. Applicants argue that CAPON is a known competitive antagonist in the binding between nNOS and PSD-95, and therefore does not meet the requirements of instant claim 1 that the compound must be screened for its ability to antagonize PDZ binding. This argument has been carefully considered but is not found persuasive.

It is recognized that the Tochio reference shares authorship with an inventor named in the instant application. Under 35 USC 102, an inventor must file an application for a patent on an invention within one year of public disclosure, i.e. publication of the method in a scientific journal, for example. Additionally, the list of named inventors must include all authors named in the published scientific paper. Therefore, under US law, it is required to reject a patent application despite Applicants' original conception and reduction to practice, if the invention has been publicly disclosed for more than one year, or if the inventorship of the patent application does not include all authors of the earlier publication. (The authorship requirement can be

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overcome if authors not included in the patent application sign a waiver stating that they should not be included.)

Applicants argue that, in fact, instant claims 1-3, 16-19, 21, and 22 do not recite identical steps as taught by the Tochio reference. Examiner respectfully disagrees. Although Tochio et al teach that the intended use of the invention is to solve the solution structure of PDZ2 of PSD-95 in both bound and unbound configurations, the steps they teach meet all the limitations of the claimed screening method. By virtue of inhibiting binding, CAPON fragments fit the definition of a neuroprotective drug. They teach that the solution structure of PDZ2 can be solved by NMR before and after binding by CAPON. They teach that CAPON elicits all the physical characteristics in PDZ2 that one would expect to observe during binding of a compound that is a neuroprotective drug. The newly-included step g) in claim 1, in which an artisan makes an assessment about said test compound's potential as a neuroprotective drug, is a purely mental step, and therefore does not patentably differentiate the instant application from the teachings of Tochio et al. In other words the physical steps recited in the instant application are identical to the physical steps taught by Tochio et al, and consideration of the meaning of collected data does not differentiate the application from the prior publication. To afford patentability to the instant claims, they must be amended to recite tangibly different physical steps, not simply changes in how the data would be considered.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-9 and 12-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tochio et al in view of Lee et al (Neuroscience Lett, 2000) and Aarts et al (Science, 2002).

This rejection is maintained for reasons of record set forth in the paper mailed 25 September 2006, and repeated below.

The teachings of Tochio et al are discussed above and applied as before. Tochio et al do not expressly teach the application of flavonoids in a method of inducing conformational changes in PDZ2 of PSD-95 that are observable by NMR.

Lee et al teach the administration of flavonoids related to the catechin molecule, which are present in green tea. Lee et al teach that it is known in the art that green tea has a protective effect against neuronal damage (see p. 191, col 2, for example) and ameliorates brain damage during ischemia (see p.192, col 2, for example), and that part of this neuroprotective effect is attributable to flavonoids. They test the effect of administration of a flavonoid, EGCG, on gerbils after during artificially-induced brain ischemia. They report that administration significantly increases the number of neurons surviving the brain injury (see Fig. 2, p. 194, for example). They speculate that part of the neuroprotective effect they observe may be due to inhibition of neuronal nitric oxide

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synthase (nNOS) activity, which plays an important role in pathophysiological processes including neurotoxicity (see p. 194, for example).

Aarts et al teach that it is well known in the art that PSD-95 binds to nNOS and NMDA receptors through its second PDZ domain (see p. 846, for example). They also teach that it is known in the art that blocking the interaction between NMDA receptors and PSD-95 (by removing PSD-95 entirely, for example) dissociates NMDA receptor from nitric oxide production and suppresses excitotoxicity, which is a cause of neuronal death and brain damage during brain injury. Aarts et al constructed a peptide that interacts with the PDZ2 domain of PSD-95, thus blocking its interaction with NMDA receptor, and introduced it into rat neurons; this peptide interacted with the endogenous, full-length PSD-95. Because of the strong similarity between rodent and human PSD-95 sequences, it is obvious that their experimental findings are attributable not just to rat neurons, but provide guidance as to the mechanism of human PSD-95, as well. They teach that this peptide inhibits nitric oxide production (determined by measuring its correlate, cyclic GMP), and enhances survival of neurons exposed to excitotoxic NMDA (see text p.847; see Fig. 2 panel E p. 848; see Fig. 3 panel A, p. 849, as examples).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to study the action of flavonoids on the conformation of PDZ2 of PSD-95 in a method of testing agents for their protective effect against brain damage, because Tochio et al teach that it is possible to use NMR to study conformational changes in PDZ2 of PSD-95 in response to a ligand, Aarts et al teach that ligand binding of PDZ2 of PSD-95 enhances neuronal survival by blocking nitric oxide



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production, and Lee et al teach that flavonoids from green tea protect against brain damage, and suggest the effect of flavonoids may be due to inhibition of nitric oxide production. One would have been motivated to do so for the expected benefit of better determining why flavonoids have a neuroprotective effect during brain injury events such as stroke.

Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, one would have had a reasonable expectation of success in practicing the claimed invention.

### ***Response to arguments - 35 USC § 103***

Applicants argue that the rejection of instant claim 1, for example, under 35 USC 103(a) is improper because the rejection is made using references that teach art that is irrelevant to the instant claims. The rejection is made because a reference that is judged to anticipate a claimed method, i.e. the Tochio reference, also renders the claimed method obvious.

### ***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

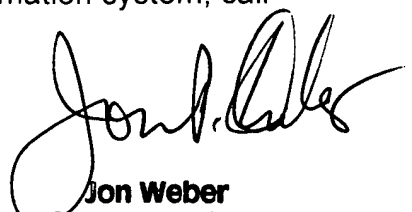
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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clark D. Petersen whose telephone number is (571)272-5358. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571)272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CDP  
3/15/2007

  
**Jon Weber**  
**Supervisory Patent Examiner**